

OVERPOWERED ABA RECEPTOR AGONISTS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application is a continuation of International Patent Application PCT/US2019/039978, which was filed Jun. 28, 2019, which claims priority to U.S. Provisional Patent Application No. 62/691,534, which was filed Jun. 28, 2018, both of which are incorporated by reference in their entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This invention was made with government support under Grant No. IOS1258175 and 1656890 awarded by the National Science Foundation. The government has certain rights in this invention.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] This application includes a Sequence Listing as a text file "SL-1144963.txt," machine format IBM-PC, MS-Windows operating system, created Jun. 28, 2019, and containing 225,426 bytes. The material contained in this text file is incorporated by reference in its entirety for all purposes.

TECHNICAL FIELD

[0004] The present invention sets forth small novel abscisic acid (ABA) receptor agonist scaffolds and compounds with potent in vivo activity. In some aspects, the present invention provides agricultural formulations and methods comprising the ABA receptor agonists described herein, such as methods of managing crop water use and improving drought tolerance. In some preferred embodiments, the inventive compounds have improved properties relative to the current "best in-class" molecules quinabactin and its derivatives.

BACKGROUND OF THE INVENTION

[0005] Absciscic acid (ABA) is a plant hormone that regulates signal transduction associated with abiotic stress responses (Cutler et al., 2010, *Absciscic Acid: Emergence of a Core Signaling Network*, Annual Review of Plant Biology 61:651-679). The ABA signaling pathway has been exploited to improve plant stress response and associated yield traits via numerous approaches (Yang et al., 2010, "Narrowing Down the Targets: Towards Successful Genetic Engineering of Drought-Tolerant Crops", *Mol. Plant*, 3(3): 469-490). The direct application of ABA to plants improves their water use efficiency (Rademacher et al., 1987, "Water consumption and yield formation in crop plants under the influence of synthetic analogues of abscisic acid," in: Hawkins et al. (ed.) "Plant growth regulators for agricultural and amenity use," BCPC Monograph 36:53-66); for this reason, the discovery of ABA receptor agonists (Park et al., "Absciscic Acid Inhibits Type 2C Protein Phosphatases via

the PYR/PYL Family of START Proteins," *Science*, vol. 324, no. 5930, pp. 1068-1071 (2009); Melcher et al., 2010, "Identification and mechanism of ABA receptor antagonism," *Nature Structural & Molecular Biology* 17(9):1102-1110) has received increasing attention, as such molecules may be beneficial for improving crop yield (Notman, "Organic compound comes to the aid of thirsty plants", Royal Society of Chemistry at <http://www.rsc.org/chemistryworld/News/2009/May/01050901.asp> (May 1, 2009; downloaded on Jun. 29, 2015)).

[0006] ABA elicits many of its cellular responses by binding to a soluble family of receptors called PYR/PYL proteins. PYR/PYL proteins belong to a large family of ligand-binding proteins named the START superfamily (Iyer et al., 2001, "Adaptations of the helix-grip fold for ligand binding and catalysis in the START domain superfamily," *Proteins: Structure, Function, and Bioinformatics* 43(2):134-144); Ponting et al., 1999, "START: a lipid-binding domain in StAR, HD-ZIP and signalling proteins," *Trends Biochem*, 24(4):130-132). These proteins contain a conserved three-dimensional architecture consisting of seven anti-parallel beta sheets, which surround a central alpha helix to form a "helix-grip" motif, together, these structural elements form a ligand-binding pocket for binding ABA or other agonists.

[0007] The first synthetic ABA receptor agonist identified was pyrabactin (Park et al., op. cit.), a naphthalene sulfonamide that efficiently activates ABA signaling in seeds, but has limited activity in vegetative tissues, where the most critical aspects of abiotic stress tolerance occur. Sulfonamides highly similar to pyrabactin have been disclosed as ABA receptor agonists (see U.S. Pat. App. Pub. No. 2013/0045952) and abiotic stress modulating compounds (see U.S. Pat. App. Pub. No. 2011/0230350). Non-sulfonamide ABA receptor agonists have also been described (see U.S. Pat. App. Pub. Nos. 2013/0045952 and 2011/0271408).

[0008] Other synthetic agonists have been described including quinabactin (QB, Okamoto et al.) and cyanabactin (CB, Vaidya et al.). These compounds are similar in possessing two hydrophobic ring systems connected by a sulfonamide linker. Despite extensive research, there have been no synthetic ABA mimics discovered or designed that can activate all ABA receptors. Furthermore, quinabactin and a recently described derivative AMF4 possess relatively low persistence anti-transpirant activity across multiple species and low bioactivity in *Lycopersicon esculentum*, an important crop species. Persistence is an important feature that determines the duration of anti-transpirant effects. In some embodiments, the present invention sets forth highly potent and persistent "overpowered" ABA receptor agonists developed by structure based optimization of a new non-sulfonamide scaffold discovered by virtual screening.

BRIEF SUMMARY OF THE INVENTION

[0009] In some aspects, the invention presents a method of increasing stress tolerance in a plant, the method comprising contacting the plant with a sufficient amount of a compound to increase stress tolerance in the plant compared to not contacting the plant with the formulation;